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A parallel high-throughput approach to liquid crystal screening

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A technique has been developed for the high-throughput (HT) parallel screening of liquid crystal (LC) phase transitions, using optical anisotropic effects observed only in the LC state to allow the determination of melting and clearing points. A camera was used to monitor optical changes observed in arrays of LC samples upon heating, when illuminated with plane polarized light and viewed through a second polarizer aligned perpendicular to the plane of polarized light. Data was processed using Image Pro Plus, extracting values for the melting point and clearing point of each sample in the array. When compared with literature and conventional differential scanning calorimetry the new technique was found to be in excellent agreement, establishing the technique as a viable HT alternative. The method was used to analyze a 75 formulation library prepared using liquid handling for HT clearing point determination, showing the scope and power of the technique in the analysis of larger libraries. © *2005 American Institute of Physics.* [DOI: 10.1063/1.1906125]

I. INTRODUCTION

The synthesis of large numbers of liquid crystals (LCs) has been pursued for many years in an attempt to gain structure property relationships and to develop specific properties for uses in commercial applications such as liquid crystal displays[1] (LCDs). The application of high-throughput (HT) methods to the synthesis of liquid crystal libraries is relatively recent; however success has been found using combinatorial methods to introduce diversity into to a central core so that structure property relationships can be explored. Deeg[2,3] applied a solution phase parallel synthetic route with parallel purification to produce a library (225 members) of 4,4‴-dipropyl-*p*-quaterphenyl liquid crystal homologes in high yield. Goulding[4] demonstrated the solution phase, one pot synthesis of multiple 4-alkyl-4′ cyanobiphenyls while Hioki[5] developed the solid phase parallel synthesis of a 28 member azomethine-linked liquid crystal library. Kang[6] prepared a 40 member library by the coupling of resorcinol derivatives, 4-formylbenzoic acids and 4-alkoxyanalines, to form bent- shaped mesogens. To assess LC properties of the resulting libraries a screening process must be employed. In traditional libraries[7–11] a combination of optical polarizing microscopy followed by differential scanning calorimetry (DSC) is routinely used to identify and confirm the presence of phase transitions. Although these techniques are well established and accurate and can be used to distinguish a wide range of liquid crystalline phases, they are time consuming and can only be performed on single compounds. In the screening of a large library this severely restricts a rapid discovery process, limiting the formulation of new LCs, which is the major route to optimizing new LC materials, and thus provides a major obstacle when larger libraries need to be considered.

To date, no methods have been developed that are suitable for HT LC screening, although recently hyper DSC[12,13] techniques have emerged, allowing increased throughput of samples using faster thermal scan rates. In materials combinatorial chemistry HT screening can take many forms depending on the application, usually requiring adaptation of conventional analytical tools or the development of novel methods.[14] Optical imaging is often employed as a tool, demonstrated in the HT screening of ternary-metal-alloy libraries,[15] imaging of phosphor discovery libraries by UV excited photoluminescence[16,17] and screening of catalyst libraries by IR imaging.[18] A device was therefore designed and built that would allow the HT formulation and analysis of liquid crystal libraries.

II. DEVELOPMENT OF A HIGH-THROUGHPUT LC SCREENING DEVICE

One of the initial parameters to be explored in a LC library is the liquid crystal range defined at the lower end by its melting point and at the upper end by the transition from a liquid crystal to an isotropic liquid, referred to as the clearing point. While within this range many mesophases can exist, depending on the structure of the LC. The drawback to the traditional technique of determining mesophases, using DSC followed by polarized optical microscopy, is that the

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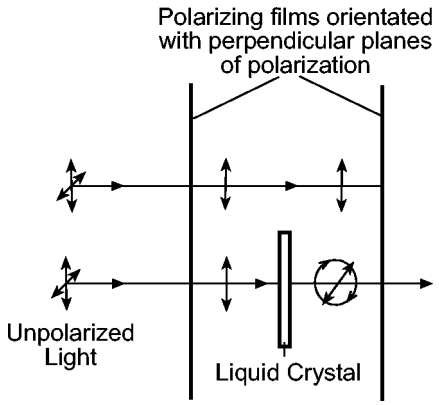

FIG. 1. The path of unpolarized light through a pair of perpendicularly aligned linear polarizers showing the interaction when a sample of liquid crystal is introduced. Normally light which has been linearly polarized in one plane cannot pass the second polarizer, however the presence of an optically anisotropic liquid crystal between the polarizers causes linearly polarized light to become circularly polarized and able to pass through the second film.

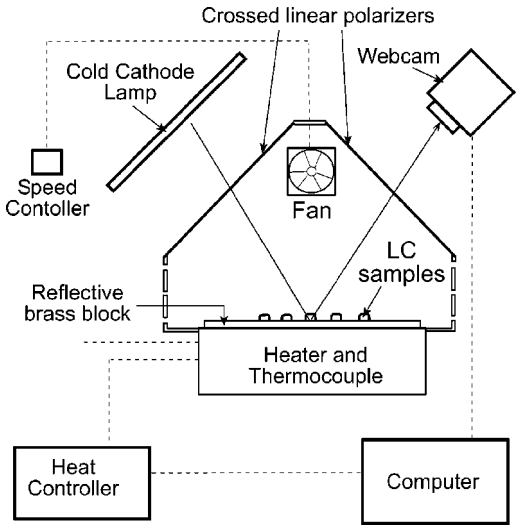

FIG. 2. Schematic of the high-throughput screening apparatus for liquid crystal phase transitions.

time taken for screening can exceed the time taken for synthesis and/or formulation. The development of a device able to measure both melting and clearing points of LC substances in parallel would allow large libraries to be screened quickly, allowing the rapid identification of materials with desirable LC properties for further in-detail characterization.

In the design of the HT device, a property which is exhibited only in the liquid crystalline phase was exploited, allowing the phase transition from solid to LC and LC to isotropic liquid to be determined. Optical anisotropy causes the circular polarization of linear polarized light as it passes through the material, a result of light traveling at different speeds through the material depending on its orientation in relation to the optical axis, in this case the LC director. As a consequence the emerging ordinary and extraordinary rays come out of phase, causing a change in polarization.

To visualize this effect two polarizers can be placed, with their plane of polarization at 90° to each other, on either side of a LC sample. One side of the apparatus is illuminated and the opposite side is then observed as shown in Fig. 1. In the area where there is no LC sample there will be no light transmitted due to the polarizing films and hence it will appear dark. In contrast, light which passes through the LC sample loses its linear polarization and is transmitted through the second polarizer, to be observed as a light area through the film.

It was this principle that was the basis for the HT screening device for determining LC melting and clearing points. As only the LC phase possesses anisotropic properties, solids and isotropic liquids will not be seen through the crossed polarizers. As the temperature is increased and the LC mesophase begins to form the sample will appear as a white spot. As the temperature is increased further a phase change to an isotropic liquid will occur and the sample would be observed to disappear as its anisotropic properties are lost. Thus by analysis of the temperatures at which this change occurs, the melting and clearing points of the LC sample can be determined. Mesophases that occur between the melting and clearing points, such as smectic phases, can also be identified by a change in intensity of the white spot.

III. DESCRIPTION OF APPARATUS

The HT LC screening device (in Fig. 2), consisted of a heating block containing a thermocouple which provided feedback to a Calcomms 3300 temperature control unit for thermostatic control, interfaced to a PC to provide data logging. Mounted to the top of the heating element was a 100 mm×100 mm×5 mm brass block, chrome plated to provide a resilient and reflective surface for sample loading. To the top face of the heating block was mounted a removable enclosure, designed to hold two sheets of polarizing film in a fixed angled position above the heating block, the angle and height of the enclosure optimized so that the reflection of the opposite polarizing film on the chrome block could be observed when looking into the enclosure through one film. The films were aligned with the plane of polarization at 90° to each other, and to ensure optimum extinction the polarizers could be rotated by 3° each way. To prevent the buildup of heat and damage to the polarizers inside the enclosure a fan was fitted, while holes were made in the front and back of the enclosure for cooling. The whole unit was painted matte black to prevent the ingress of any unpolarized light which could reduce the sensitivity of the apparatus. Above the heating block and enclosure setup and above one polarizing film was fixed a cold cathode backlight, to provide an intense homogenous light source, and a webcam above the other. The webcam was aligned such that the reflection of the second film could be seen and was interfaced to a PC to provide image capture.

The HT screening device was calibrated externally using a digital surface thermometer that was attached to the surface of the brass block with thermal paste and the the Calcomms controller was adjusted to match the temperature while an IR thermal camera (IRRIS 256ST) was used to measure temperature uniformity. The IR images in Fig. 3 show a variation in temperature of approximately 2.5–3 °C from the center of

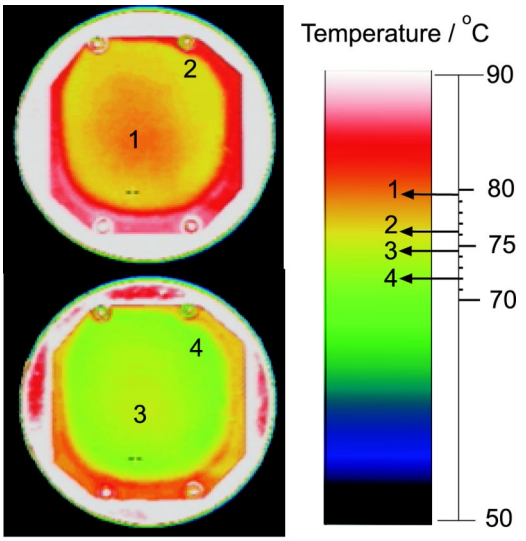

FIG. 3. (Color online) IR images of the high-throughput screening hot-plate. The thermal distribution was measured by analysis of the temperatures at the outer and inner sections of the heating plate. Analysis is carried out in duplicate and found to differ by 2.5–3 °C from the center to the edge of the plate. At the extremes of the plate lies a high-temperature area which should not be used for sample analysis.

the heating block to the outer edge, and a high temperature ring on the extreme edges, which could not be used for sample analysis. Other settings were configured automatically using the auto setup routine of the Calcomms instrument.

IV. SAMPLE LOADING

LC samples are loaded onto the apparatus in one of two ways. For smaller numbers (<50), samples could be spotted, using a pipette, directly onto the chromed plate. For larger numbers of samples (50–100) this method was not suitable as the sample density was too high, resulting in the amalgamation of sample spots upon heating, and therefore a method of sample containment was used by application of a contact photolithography process reported by Cabral[19] and Harrison.[20] In this process a UV cured adhesive (Norland, NOA81) was cast into a 10×10 grid with 2.5 mm $\times$2.5 mm wells produced on a 32 mm$\times$32 mm cover slide. The wells were filled and the slide placed onto the surface of the chromed plate. Figure 4 shows an example of the LC samples loaded onto the plate directly [Fig. 4(a)] and in the microwell array [Fig. 4(b)] as visualized by the webcam. Containment also facilitates later analysis as the positions of samples are fixed throughout the data collection sequence. LC's anisotropic effects are usually only seen when the director is orientated by a alignment layer or an external field. In this example the natural alignment of the LC's on either the chrome or the glass surface appeared sufficient to observe the anisotropic effects, eliminating the need for an additional surface alignment layer.

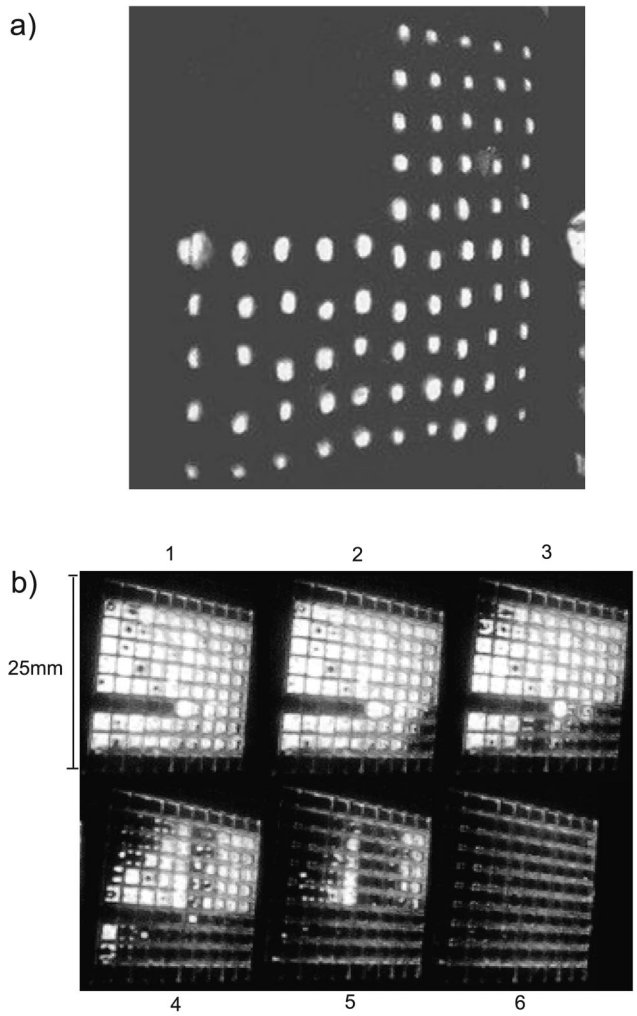

FIG. 4. Images of liquid crystal samples loaded onto the high-throughput screening apparatus for liquid crystal phase transitions, as seen through perpendicularly aligned linear polarizers. (a) Samples spotted directly onto the analysis surface. (b) Samples loaded into a "well" matrix, prepared using a contact photolithography process. The glass coverslip is then placed onto the analysis surface. 1=25 °C, 2=80 °C, 3=100 °C, 4=115 °C, 5=130 °C, and 6=150 °C.

V. PROCEDURE FOR MEASUREMENT OF MELTING AND CLEARING POINTS

Following sample loading the apparatus was assembled and the webcam arranged to give optimal images of the LC samples. The samples were heated from 25 °C and 160 °C at a rate of 5 °C/min, the fastest heating rate available which produced a linear response throughout the temperature range, while data was collected from both the webcam and the Calcomms controller simultaneously. Images from the webcam were recorded at 1 frame per second, producing a video sequence of the intensity change while the temperature was recorded at 4 s intervals. Figure 4(b) shows a sequence of images as materials pass the clearing point on the apparatus and become transparent. The presence of monotropic and enatiotropic LC phases was determined by data collection throughout the cooling cycle.

The resulting video sequence was analyzed using the image analysis software Image Pro Plus, sampling every

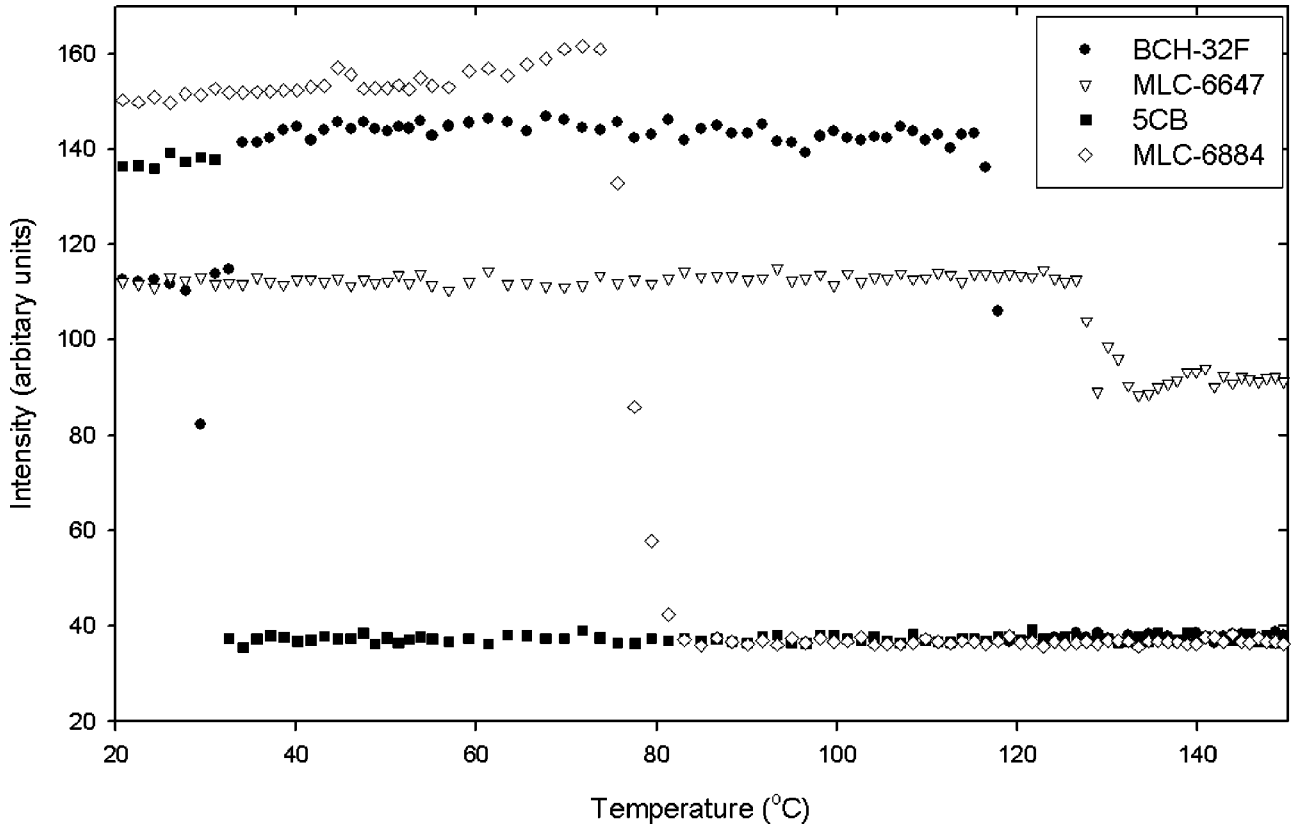

FIG. 5. Selected experimental data obtained from the high-throughput screening apparatus for liquid crystal phase transitions. For clarity the number of data points has been reduced by a factor of 3. Liquid crystal transitions can be seen as steps in the data. An Increase in intensity occurs due to a crystalline to nematic transition and a decrease in intensity due to a nematic to isotropic transition.

third frame to reduce the number of data points and speed up processing. Image pro plus allows items to be defined by their location on the video sequence and allows the measurement of white intensity (as an integer between 0 and 255); using these integral functions the coordinates of each sample spot on the first frame of the video sequence were defined and their intensity determined. The sequence was then advanced and the intensity of each spot at each frame in the sequence recorded automatically in an Excel spreadsheet to allow a plot of intensity versus temperature to be produced. Figure 5 shows data for four selected compounds, with phase transitions being seen as discontinuities in the data.

VI. PROCESSING

The data were processed to ease identification of phase transitions and eliminate noise from fluctuations in background light levels over the course of the experiment by evaluating the change in intensity between each set of points. A scatter plot was then produced with the phases easily identified by the points at which the data is nonlinear and moves significantly from the standard. In cases where the transition was particularly sharp and hence there was only one data point with which to identify the transition, the clearing or melting point could also be identified as the first data point at which the intensity drops, using the graph in Fig. 5. Figure 6 shows the averaged data from three LCs. The transitions can be identified clearly by the sharp peaks above or below the normal line. The standard deviation is also shown in Fig. 6 as two thin horizontal lines. The fact that these peaks, corresponding to phase transitions, lie significantly above or below this line shows that the event is significant and not a result of experimental error.

VII. EXPERIMENTAL RESULTS

To validate the technique a range of well-known commercially available LCs (Merck) were analyzed using this

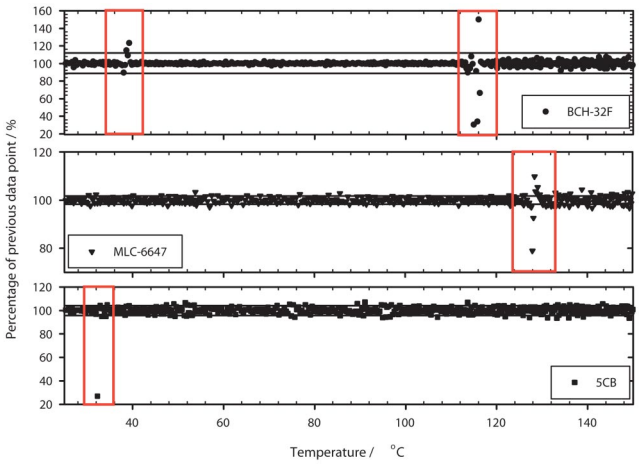

FIG. 6. (Color online) Averaged experimental data obtained from the high-throughput screening apparatus for liquid crystal phase transitions. By treatment of the data in this way phase transitions can be easily observed. Large deviations from 100% identify the locations of phase transitions, as highlighted. The standard deviation can be seen as the two horizontal lines running above and below the data.

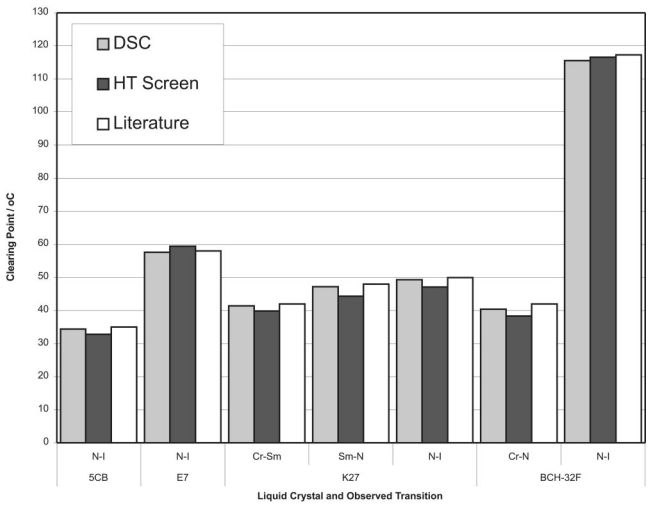

FIG. 7. A comparison of the high-throughput screening apparatus for liquid crystal phase transitions and conventional DSC analysis, compared with those given in the literature. The mesophases observed in the liquid crystal samples are crystalline to nematic (Cr-N), nematic to isotropic (N-I), crystalline to smectic (Cr-Sm), and smectic to nematic (Sm-N).

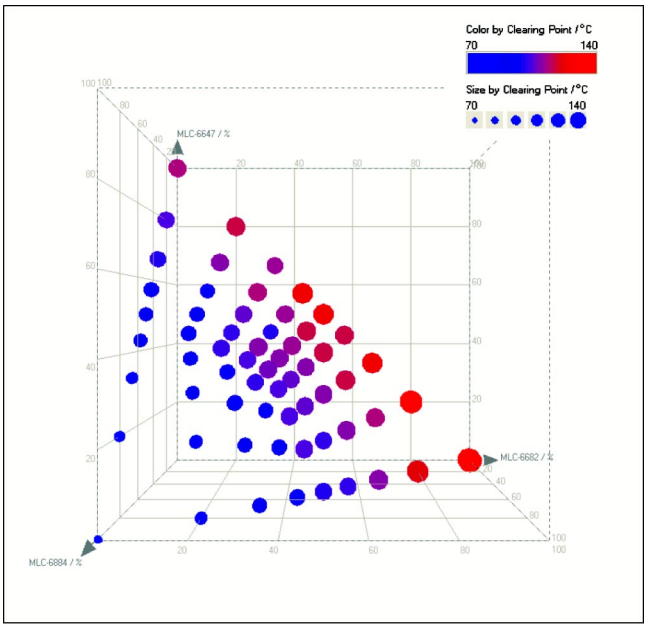

FIG. 8. (Color online) The relationship between the composition of a mixture, formulated from three components and its clearing point as obtained from the high-throughput screening apparatus for liquid crystals. The clearing point is visualised in the fourth dimension using color and size.

HT apparatus. Thirteen compounds with a wide range of phase transitions including crystalline to nematic (Cr-N), nematic to isotropic (N-I), crystalline to smectic (Cr-Sm), and smectic to nematic (Sm-N) were analyzed and selected results are shown in Fig. 7. The transition temperatures were compared with values obtained from conventional DSC analysis of the same materials (taking the onset temperature as the phase transition) and those gained from the literature.[21] The results were in complete agreement (within experimental error), establishing this method as a viable alternative to DSC for library screening. The time taken to run the HT experiment equates approximately to the time taken to run a single LC sample by conventional DSC and the results were found to be highly reproducible. The presence of smectic mesophases could be detected although they could not be classified as such in isolation. In Fig. 7 the smectic phase of K27 was classified because this is a known compound, in the case of an unknown material the presence of a second or third mesophase would only be identified, not defined. As with DSC, full classification must come from analysis using polarized optical microscopy.

VIII. SCREENING OF MIXTURE LIBRARIES

A large percentage of the LC materials produced annually are used in the manufacture of LC display (LCD) devices, and such displays contain a complex mixture of individual components chosen and blended to provide properties that match exact specifications. In addition to the screening of LC synthesis libraries there is great interest in the screening of LC mixture libraries using the same methods, as the continued advance in LCD technology drives the demand for mixtures with more demanding properties. To formulate such a mixture requires an understanding of the effect a LC will have on bulk properties. Traditionally this is explored by manually mixing and analyzing individual mixtures, however, with the development of HT screening and the use of robotic liquid handling, productivity is increased and large mixture libraries can be formulated and tested in a matter of hours.

To illustrate this approach a library of 75 mixtures was constructed using three commercially available materials. The components were each dissolved in DCM (1:1 volume ratio) to reduce viscosity before robotically dispensing predetermined volumes of the materials into a 96 well plate, producing mixtures where each of the three components was present at between 0 and 100% of the overall volume. The solvent was removed by evaporation at room temperature h and then, to ensure complete removal, without elimination of the more volatile components of the mixture, heated at 80 °C for 5 min. The library was loaded into the microwells of the contact photolithography matrix and heated from 25 °C to 160 °C. The data collected was visualized in Fig. 8 as a four-dimensional plot relating the % composition of each component to its clearing point (the fourth dimension represented using color and size).

The mixtures showed, as expected, a linear relationship with composition of the three components, showing the apparatus to be a powerful tool in identifying the phase transitions of mixture libraries. To validate the accuracy of the recorded phase transitions, the clearing point for each component at 100% was compared with literature[21] values and found to be in good agreement: transition by HT screen (transition from literature), MLC-6682: 74.9 °C (74.5 °C), MLC-6647: 114.7 °C (111.0 °C), and MLC-6884: 134.9 °C (133.5 °C).

IX. DISCUSSION

The development of a HT screening technique for LC phase transitions, which provides comparable results to con-

ventional DSC data, has shown that LC synthesis or formulation libraries can be analyzed in a fraction of the time compared with conventional methods. The technique can be applied to small or large libraries consisting of single LC components or simple or complex LC mixtures and was found to be accurate and reproducible in all cases.

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